UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 11-APR-2008

Subject: **Isoxaflutole**. Application for Registration of Two New Products for Use on Corn: SC 465 Herbicide and SC 480 Herbicide. Summary of Analytical Chemistry and Residue Data. Decision Nos. 379124 and 379125; 40 CFR 180.537.

PC Code: 123000
MRID Nos.: 44169006, 44436001, 44506301, 45655902, 45655909, 47114034 and 47114035
Petition No.: None

Assessment Type: None
TXR No.: None

DP Nos.: 340598, 340678
Registration Nos.: 264-RNAT, 264-RNAA
Regulatory Action: Section 3 Registration
Reregistration Case No.: None
CAS No.: 141112-29-0

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This document was originally prepared under contract by Dynamac Corporation (2275 Research Blvd, Suite 300; Rockville, MD 20850; submitted 02/08/2008). The document has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

Executive Summary

Isoxaflutole is an isoxazole herbicide (Group 27) registered for control of broadleaf and grass weeds in corn. Bayer CropScience has developed a new herbicide safener (AE 0001789; cyprosulfamide) for use on corn in conjunction with isoxaflutole. Bayer is requesting registration of two new isoxaflutole products for use on corn: SC 480 Herbicide (EPA File Symbol No. 264-RNAT), a 2.0 lb/gal suspension-concentrate (SC; equivalent to a flowable-concentrate, FlC) formulation also containing the safener cyprosulfamide at 2 lb/gal; and SC 465 Herbicide (EPA File Symbol No. 264-RNAA), a 1.88 lb isoxaflutole/gal FlC formulation also containing the safener, at 1.25 lb/gal, and a new active ingredient (thiencarbazone-methyl), at 0.75 lb/gal. The

products are proposed for a single application to corn as a preplant, preemergence, or early postemergence application at a maximum rate of 0.141 lb ai/A, with a 45-day preharvest interval (PHI) for postemergence application. No changes to the existing tolerances for isoxaflutole residues have been proposed.

Evaluation of residue data for the safener and the new active ingredient is the subject of separate data reviews (see DP#s 341999 and 339779, respectively). Generally, the amount of a safener in pesticide products is considered to be Confidential Business Information (CBI). However, in the case of these products, the amount of cyprosulfamide in each product is stated on the labels (in the "Use Restrictions and Precautions" section). Therefore, it is not necessary to treat the cyprosulfamide concentration as CBI for any of the products.

Tolerances have been established for residues of isoxaflutole under 40 CFR §180.537. Tolerances are currently established under 180.537(a)(1) for combined residues of isoxaflutole and its metabolites 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propan-1,3-dione (RPA 202248) and 2-methylsulphonyl-4-trifluoromethyl benzoic acid (RPA 203328), calculated as the parent compound, in/on field corn forage, grain, and stover, at 1.0, 0.20, and 0.50 ppm, respectively. Tolerances have also been established under 180.537(a)(2) for combined residues of isoxaflutole and RPA 202248, calculated as the parent compound, in livestock commodities at 0.01 ppm for egg; 0.02 ppm for milk; 0.10 ppm for the meat byproducts, except liver, of cattle, goat, hog, horse, and sheep; 0.20 ppm for the fat and meat of cattle, goat, hog, horse, poultry, and sheep; 0.30 ppm for poultry liver; and 0.50 ppm for the liver of cattle, goat, hog, horse, and sheep.

The nature of the residues in corn is understood, based on metabolism studies with corn treated with isoxaflutole with and without the safener cyprosulfamide. The residues of concern in field corn commodities, for both tolerance expression and risk assessment, are isoxaflutole and its metabolites RPA 202248 and RPA 203328. The nature of the residue in livestock is understood based on metabolism studies with goats and hens. The residues of concern in livestock for tolerance enforcement are isoxaflutole and RPA 202248; for risk assessment, the residues of concern are isoxaflutole, RPA 202248, RPA 205834, and RPA 207048.

An adequate gas chromatography/mass-selective detector (GC/MSD) method is available for the enforcement of tolerances for crop commodities. The method is a common moiety method which determines total residues of isoxaflutole, RPA 202248, and RPA 203328; the limit of quantitation (LOQ) is 0.01 ppm. An adequate high-performance liquid chromatography/ultraviolet (HPLC/UV) method is available for the enforcement of tolerances for livestock commodities. The method determines residues of isoxaflutole and RPA 202248 in milk and eggs separately, and determines combined residues of isoxaflutole and RPA 202248 in tissues using a common moiety technique. The LOQs are 0.01 ppm for milk and eggs, 0.20 ppm for beef and poultry muscle and fat, 0.20 ppm for beef kidney, and 0.40 ppm for beef and poultry liver.

Adequate crop field trial data were submitted to support the proposed uses. Following application of an FlC formulation of isoxaflutole plus safener cyprosulfamide to corn as an early postemergence application, combined residues of isoxaflutole, RPA 202248, and RPA 203328 in/on field corn forage, grain, and stover did not exceed the established tolerances for these commodities. **No changes to the tolerances for field corn commodities are required to**

support the proposed uses. HED notes that due to highly variable recoveries, the version of the method used in these trials is unsuitable for tolerance enforcement. The residue data generated with version of the method is also not adequate for tolerance-setting purposes, but is adequate to demonstrate that residues will not exceed the established tolerances.

Adequate livestock feeding study data have been submitted previously. The established tolerances for residues of isoxaflutole and RPA 202248 in livestock commodities were based on the results of these studies. Because the proposed uses do not require any changes to the tolerances for field corn commodities, the proposed uses do not affect the theoretical dietary burden of isoxaflutole to livestock. Therefore, no changes to the established tolerances for livestock commodities are required to support the proposed uses.

Adequate confined and field rotational crop studies have been submitted previously; the residues of concern in rotational crops are isoxaflutole and its metabolites RPA 202248 and RPA 203328. These data indicated that plantback intervals (PBIs) of 4 months for wheat and 6 months for all other crops are appropriate for isoxaflutole; no rotational crop tolerances are required. The proposed rotational crop restrictions for the two new products are adequate.

Regulatory Recommendations and Residue Chemistry Deficiencies

Pending submission of a revised Section B (see requirements below), there are no residue chemistry issues that would preclude granting an unconditional registration for the requested uses of isoxaflutole.

860.1200 Directions for Use

- The proposed PHI of 45 days for grain and stover is not supported by the field trial data. Because the product labels specify that applications may not be made after the V2 growth stage of corn, a PHI is not needed for the grain and stover of field corn. The petitioner should modify the labels to clarify that the 45-day PHI pertains only to corn forage.

- On the label for SC 465 Herbicide, rotational crop restrictions have been provided for total application rates greater than 0.033 lb ai/A. Rotational crop restrictions for total application rates less than the specified rate should also be proposed.

- The label for the SC 480 Herbicide should be modified to clarify an apparent contradiction in the "Preplant Surface-Applied" application directions and the "Restrictions and Precautions for Use" section. The restrictions section specifies that only one application may be made to corn per season. The instructions for preplant surface-applied application specify that the application may be split, with 60% of the recommended rate applied prior to planting and the remaining 40% applied at planting. If the petitioner wishes to allow split preplant/at-planting applications, then the restrictions section should be modified accordingly.

- The label for the SC 465 Herbicide and SC 480 Herbicide recommends the use of spray adjuvants for early postemergence applications. This recommendation should be

removed from the proposed label, as the submitted crop field trial data did not reflect the use of spray adjuvants in the application mixtures.

Background

Isoxaflutole is an isoxazole herbicide (Group 27) registered for control of broadleaf and grass weeds in corn. Bayer CropScience has developed a new herbicide safener (cyprosulfamide) for use on corn in conjunction with isoxaflutole. Residue chemistry data to supporting the existing uses of isoxaflutole on field corn were submitted under PP#5G4484 and PP#6F04664, and reviewed by HED previously (see DP#s 214199 and 214212, 12/7/95, P. Errico; DP# 224213, 8/14/96, G.F. Kramer; DP# 232139, 7/14/97, G.F. Kramer).

The chemical structure and nomenclature of isoxaflutole and its metabolites RPA202248 and RPA 203328 (and the safener cyprosulfamide) are presented in Table 1. The physicochemical properties of the technical grade of isoxaflutole are presented in Table 2.

Table 1. Isoxaflutole Nomenclature.

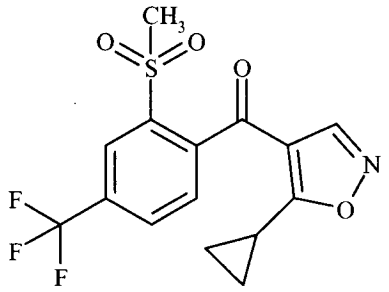
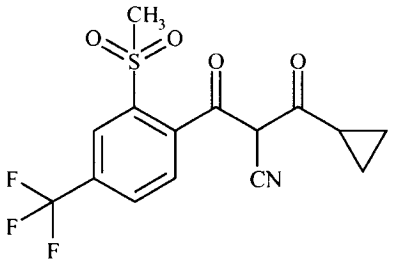
Chemical structure of parent	
Common name	Isoxaflutole
Company experimental name	RPA 201772; AE B197278
IUPAC name	5-cyclopropyl-4-(2-mesyl-4-trifluoromethylbenzoyl)isoxazole
CAS name	(5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone
CAS registry number	141112-29-0
End-use product (EP)	SC 480 Herbicide (EPA File Symbol No. 264-RNAT; 2.0 lb/gal FlC formulation) SC 465 Herbicide (EPA File Symbol No. 264-RNAA; 1.88 lb/gal FlC formulation)
Chemical structure of regulated metabolite	
Common name	Isoxaflutole diketonitrile; RPA 202248
Chemical name	1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione

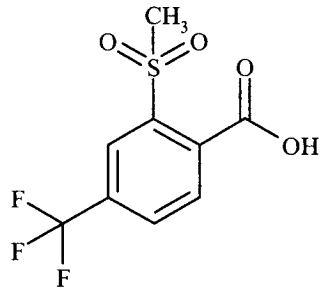
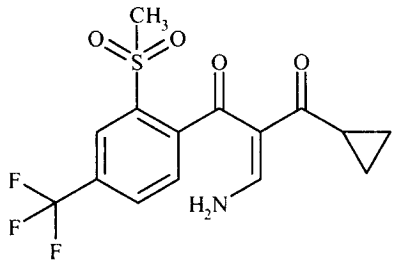
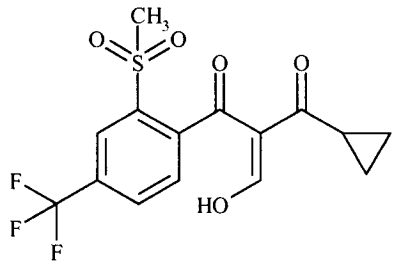
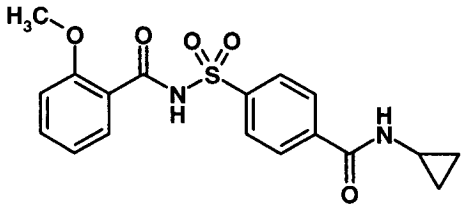
Table 1. Isoxaflutole Nomenclature.	
Chemical structure of regulated metabolite	
Common name	Isoxaflutole acid; RPA 203328
Chemical name	2-methylsulfonyl-4-trifluoromethyl benzoic acid
Chemical structure of metabolite included in risk assessment for livestock commodities	
Common name	RPA 205834
Chemical structure of metabolite included in risk assessment for livestock commodities	
Common name	RPA 207048
Chemical structure of safener	
Common name	Cyprosulfamide; AE 0001789
Chemical name	*N*-[[4-[(cyclopropylamino)carbonyl]phenyl]sulfonyl]-2-methoxybenzamide

Table 2. Physicochemical Properties of Isoxaflutole.		
Parameter	Value	Reference
Melting point/range	135-136 °C	DP#s 214199 & 214212, 12/7/95, P. Errico
pH	4.6 at 25 °C (1% w:v aqueous suspension containing 2% acetonitrile, v:v)	
Density	1.416 at 20 °C	
Water solubility	6.2 mg/L at 20 °C (pH 5.5)	
Solvent solubility	Solvent / g/L at room temperature Methylene chloride 346 Acetone 293 Acetonitrile 233 Ethyl acetate 142 Toluene 31.2 Methanol 13.8 Octanol 0.76 Hexane 0.1	
Vapor pressure	1.0×10^{-6} Pa at 20 °C	
Dissociation constant, pK_a	Not determined	
Octanol/water partition coefficient, $Log(K_{OW})$	219 (log P = 2.34) at 20 °C	
UV/visible absorption spectrum	$\lambda_1 = 204$ $\lambda_2 = 269$	MRID 47114035

860.1200 Directions for Use

Bayer CropScience is proposing to register two new products containing isoxaflutole and the safener cyprosulfamide for use on field corn as preplant, preemergence, and early postemergence applications. Information pertaining to the proposed end-use products is presented in Table 3. A summary of the proposed use patterns is presented in Table 4. The proposed rotational crop restrictions are listed in Table 5.

Currently, products containing isoxaflutole (without safener) are registered for use on field corn as preplant or preemergence applications at total seasonal rates of 0.19 lb ai/A; postemergence applications are prohibited on the current labels.

Table 3. Summary of Proposed End-Use Products.

Trade Name	EPA File Symbol No.	Isoxaflutole Concentration	Formulation Type	Target Crops	Target Pests	Label Date
SC 465 Herbicide	264-RNAA	1.88 lb/gal[1]	FlC	Field corn and corn grown for silage	Annual grass and broadleaf weeds	4/16/07
SC 480 Herbicide	264-RNAT	2.0 lb/gal[2]	FlC	Field corn and corn grown for silage	Annual grass and broadleaf weeds	4/16/07

[1] SC 465 Herbicide also contains the safener cyprosulfamide at 1.25 lb/gal and new active ingredient thiencarbazone-methyl at 0.75 lb/gal.

[2] SC 480 Herbicide also contains the safener cyprosulfamide at 2.0 lb/gal.

Table 4. Summary of Directions for Use of Isoxaflutole.[1]					
Applic. Timing, Type, and Equipment	Trade Name; Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)
Field corn and corn grown for silage					
Preplant Surface-applied or incorporated Ground	SC 465 Herbicide 1.88 lb/gal FlC [264-RNAA]	0.049 (coarse soils with ≤2.0% OM) 0.066-0.082 (coarse soils with >2.0% OM, medium, and fine soils)	1	0.141 (from all sources)	NS
Preplant/preemergence burndown Ground					NS
Preemergence during or after planting Ground					NS
Early postemergence Ground					45
Use Directions and Limitations: Use on popcorn and sweet corn is prohibited. Use limited to field corn and corn grown for silage in the states of AR, CO, IL, IN, IA, KS, KY, MO, MT, NE, ND, OH, OK, PA, SD, TN, TX, and WY. Preplant application may be made up to 21 days prior to planting. Preemergence application may be made during planting or after planting. Early postemergence application may be made to corn from spiking through 2-leaf collar growth stage (V2, the first leaf has a rounded tip). Applications are to be made in a minimum of 10 gal/A using ground equipment; aerial application is prohibited. The use of spray adjuvants (COC, methylated seed oil, non-ionic surfactant) is recommended for preplant/preemergence burndown and early postemergence applications.					
Preplant Surface-applied or incorporated Ground	SC 480 Herbicide 2.0 lb/gal FlC [264-RNAT]	0.047-0.141 (application rate is dependent on soil texture, %OM, and timing of application)	1	0.141 (from all sources)	NS
Preplant/ Preemergence burndown Ground					NS
Preemergence during or after planting Ground					NS
Early postemergence Ground					45
Use Directions and Limitations: Use limited to field corn and corn grown for silage in the states of AR, CO, IL, IN, IA, KS, KY, MO, MT, NE, ND, OH, OK, PA, SD, TN, TX, and WY. Preplant application may be made up to 21 days prior to planting; surface applied application may be split with 60% applied preplant and 40% applied at planting. Preemergence application may be made during planting (behind the planter after furrow closure) or after planting. Early postemergence application may be made to corn from spiking through 2-leaf collar growth stage (V2, the first leaf has a rounded tip). Applications are to be made in a minimum of 10 gal/A using ground equipment; aerial application is prohibited. The use of spray adjuvants (COC, methylated seed oil, non-ionic surfactant) is recommended for preplant/preemergence burndown application.					

[1] NS = Not specified. OM = Organic matter. COC = Crop-oil concentrate.

For both formulations, the use directions specify: (1) the products may be used in either conventional, conservation tillage, or no-till crop management systems; (2) applications may be made alone or as a tank mix with other herbicides; with all tank mix partners, directions for use, precautionary statements, geographic restrictions, and other restrictions on the tank mix partner

label must be followed; (3) application through any type of irrigation system is prohibited; and (4) a restricted-entry interval (REI) of 12 hours.

Table 5. Summary of Rotational Crop Restrictions on Proposed Product Labels.

Trade Name; Formulation [EPA Reg. No.]	PBI	Crop	Precipitation requirement[1]
SC 465 Herbicide 1.88 lb/gal FlC [264-RNAA][2]	0 months	Field corn[3]	None
	4 months	Wheat	None
	9 months	Barley, soybean,[3] sweet corn,[3,4] popcorn[3,4]	15 inches of cumulative precipitation from application to planting of rotational crop
	17 months	Alfalfa,[4] green and dry beans,[4] oats,[4] sorghum,[5] sunflower,[4] canola,[4] potato,[4] sugar beet,[4] and all other crops[4]	30 inches of cumulative precipitation from application to planting of rotational crop
SC 480 Herbicide 2.0 lb/gal FlC [264-RNAT]	0 months	Corn (field)	None
	4 months	Wheat	None
	6 months	Soybeans, barley, sweet corn, popcorn, potato, grain sorghum, and sunflower	None
	10 months	Alfalfa	15 inches of cumulative precipitation from application to planting of rotational crop.
	10 months	Dry beans and sugar beets; east of the Mississippi river	
	18 months	Dry beans and sugar beets; west of the Mississippi river	
	18 months	All other crops	

[1] The amount of cumulative precipitation required before planting a rotational crop is in addition to the required rotational interval given in months. Furrow or flood irrigation not to be included in total. No more than 7 inches of overhead irrigation included in total.

[2] For SC 465 Herbicide used at rates greater than 0.033 lb isoxaflutole/A. If the corn crop treated with SC 465 Herbicide is lost, only field corn may be replanted immediately; a second application of SC 465 Herbicide should not be made.

[3] Crops planted back at intervals of one year or less should not have known acute sensitivity to ALS-inhibiting and/or SU herbicides.

[4] When soil pH is 7.5 or above, crop plant back should be delayed to the next interval, and to 24 months for crops listed in the 17-month interval above.

[5] If SC 465 Herbicide was used at ≤0.033 lb isoxaflutole/A or less and the total of thiencarbazone-methyl from all sources is ≤0.0134 lb ai/A, sorghum may be planted at the 9-month or more interval.

Conclusions. The proposed labels are adequate to allow evaluation of isoxaflutole residue data relative to the proposed use. The available corn field trial data represent use of an FlC formulation of isoxaflutole containing cyprosulfamide as an early postemergence broadcast application at the V2 growth stage at ~0.12 lb ai/A. Samples of forage were collected at 43-45 days posttreatment (early forage) and at 67-118 days posttreatment. These harvest intervals support a minimum PHI of 45 days for forage. Although the crop field trial data reflect application at ~0.8x the proposed maximum seasonal rate, HED concludes that the data are adequate to support the proposed use (see 860.1500).

The harvest intervals for corn grain and stover in the crop field trials ranged 91-157 days. The proposed PHI of 45 days for grain and stover is not supported by the field trial data. Because the product labels specify that applications may not be made after the V2 growth stage of corn, a PHI

is not needed for the grain and stover of field corn. The petitioner should modify the labels to clarify that the 45-day PHI pertains only to corn forage.

On the label for SC 465 Herbicide, rotational crop restrictions have been provided for total application rates greater than 0.033 lb ai/A. Rotational crop restrictions for total application rates less than the specified rate should also be proposed.

The label for the SC 480 Herbicide should be modified to clarify an apparent contradiction in the "Preplant Surface-Applied" application directions and the "Restrictions and Precautions for Use" section. The restrictions section specifies that only one application may be made to corn per season. The instructions for preplant surface-applied application specify that the application may be split, with 60% of the recommended rate applied prior to planting and the remaining 40% applied at planting. If the petitioner wishes to allow split preplant/at-planting applications, then the restrictions section should be modified accordingly.

The label for the SC 465 Herbicide recommends the use of spray adjuvants for early postemergence applications. This recommendation should be removed from the proposed label, as the submitted crop field trial data did not reflect the use of spray adjuvants in the application mixtures.

860.1300 Nature of the Residue - Plants

DER Reference: 47114034.der.doc
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP#s 214199 and 214212, 12/7/95, P. Errico (PP#5G4484)

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-U-^{14}C]isoxaflutole (specific activity 51.1 µCi/mg) in corn when applied with the safener cyprosulfamide. The radiolabeled test substance was mixed with a SC formulation blank and the safener cyprosulfamide, diluted with tap water, and applied as a single foliar broadcast application to corn plants grown indoors in buckets. After treatment, the buckets were moved to a covered outdoor patio area. The application was made at 0.19 lb ai/A at the V2 growth stage; the application rate is 1.3x the proposed maximum seasonal rate. Samples of corn forage and sweet corn kernel plus cob with husk removed (K+CWHR) were harvested at 75 days after application (milk stage), and samples of mature corn grain and stover were harvested at maturity, 106 days after application.

Total radioactive residues (TRR) in corn matrices treated with radiolabeled isoxaflutole, determined by combustion/liquid-scintillation counting (LSC), were 0.081 ppm in corn forage, 0.010 ppm in corn K+CWHR, 0.015 ppm in mature corn grain, and 0.120 ppm in corn stover.

Extraction with water and acetonitrile (ACN) released the majority of the radioactivity from samples of all corn matrices: 92.9% TRR from corn forage, 96.3% TRR from corn K+CWHR, 77.3% TRR from mature corn grain, and 87.9% TRR from corn stover. Additional residues (<5% TRR) were released from stover samples using accelerated solvent extraction. Remaining nonextractable residues accounted for 7.1% TRR (0.006 ppm) in corn forage, 3.7% TRR (<0.001

ppm) in corn K+CWHR, 22.7% TRR (0.004 ppm) in mature corn grain, and 6.3% TRR (0.008 ppm) in corn stover. Because the petitioner normalized radioactivity levels, accountabilities were 100% in all matrices; recoveries prior to normalization were 86-115%. The extraction procedures adequately extracted the majority of residues from corn matrices. Residues were identified by HPLC, and the identity of the major metabolite was confirmed in stover extract by liquid chromatography with tandem mass spectrometry (LC/MS/MS). Because all experimental work was completed within 6 months of sample collection, supporting storage stability data are not required.

Approximately 67-73% TRR were identified in corn matrices. Isoxaflutole was not identified in any matrix. The major residue identified was RPA 203328 (isoxaflutole acid), accounting for 67.2% TRR (0.056 ppm) in corn forage, 60.9% TRR (0.005 ppm) in corn K+CWHR, 63.0% TRR (0.010 ppm) in corn grain, and 63.3% TRR (0.076 ppm) in corn stover. A portion of the RPA 203328 identified in corn forage and stover was found after base hydrolysis of aqueous soluble residues (15.4% TRR in forage and 4.1% TRR in stover). The only other identified metabolite was RPA 202248 (isoxaflutole diketonitrile), which accounted for 6.5% TRR (<0.001 ppm) in corn K+CWHR, 9.8% TRR (0.001 ppm) in mature corn grain, and 4.3% TRR (0.005 ppm) in corn stover; RPA 202248 was not identified in corn forage. The remainder of the radioactivity consisted of unknowns, totaling ≤12% TRR (≤0.014 ppm), and aqueous soluble fractions, totaling ≤26% TRR (≤0.016 ppm).

Based on the submitted corn metabolism study, the petitioner proposed that metabolism of isoxaflutole in corn proceeds via cleavage of the isoxazole ring resulting in RPA 202248, which is isomeric with the parent. RPA 203328 results from cleavage of the carbonyl bridge and loss of the complete isoxazole moiety. The same metabolites were observed in an earlier corn study (PP#5G4484) in which isoxaflutole was applied using both preplant incorporated and preemergence methods, without the addition of the safener cyprosulfamide. In that study, RPA 203328 was the major metabolite in all matrices (field corn forage, fodder, and grain), at 64-91% TRR. RPA 202248 was found in all matrices at <1% TRR, with the exception of grain from the preplant incorporated trial where RPA 202248 was found at 7.5% TRR. Isoxaflutole was not found in any matrix.

Although the submitted study did not include labeling in the isoxazole ring of isoxaflutole, HED has previously concluded that because metabolism of isoxaflutole proceeds via opening of the isoxazole ring, a study using isoxaflutole labeled in this ring will not be required (DP# 224213, 8/14/96, G. Kramer).

Conclusions. The submitted metabolism study is adequate to satisfy data requirements. HED had previously determined that the residues of concern in plant commodities are isoxaflutole and its metabolites RPA 202248 and RPA 203328. The new metabolism study indicates that no new isoxaflutole metabolites require regulation to support the proposed use.

860.1300 Nature of the Residue - Livestock

DER Reference: None
Residue Chemistry Memo DP# 238728, 9/25/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)

No new livestock metabolism studies were submitted with this registration request. A metabolism study with goats was submitted previously. Following dosing of goats with [phenyl-U-^{14}C]isoxaflutole at 1, 10, or 50 ppm for 7 consecutive days, TRR were lowest in fat and milk and highest in liver. In samples from the low-, mid-, and high-dose groups, TRR were, respectively: nondetectable, 0.093, and 0.350 ppm in milk (Day 5 sample); 0.015, 0.069, and 0.235 ppm in fat; 0.037, 0.263, and 0.927 ppm in muscle; 0.164, 0.905, and 2.12 ppm in kidney; and 0.536, 2.10, and 3.95 ppm in liver. Samples from the mid-dose group were subjected to residue characterization/identification procedures. Isoxaflutole was not found in any matrix. RPA 202248 was the major identified residue in milk and tissues, at ~24-86% TRR. Two other metabolites were identified: RPA 205834, in fat and milk only (8-18% TRR); and RPA 207048, in milk and tissues (12-26% TRR).

A metabolism study with poultry was also submitted previously. Following dosing of hens with [phenyl-U-^{14}C]isoxaflutole at 1 or 10 ppm for 14 consecutive days, TRR were lowest in egg white, fat, and muscle and highest in liver. In samples from the 1- and 10-ppm dose groups, TRR were, respectively: nondetectable and 0.015 ppm in egg white (Day-10 sample); 0.024 and 0.152 ppm in egg yolk (Day-12 sample); nondetectable and 0.028 ppm in fat; nondetectable and 0.035 ppm in muscle; 0.055 and 0.155 ppm in kidney; and 0.845 and 0.953 ppm in liver. Samples from the 10-ppm dose group were subjected to residue characterization/identification procedures. Isoxaflutole was not found in any matrix. RPA 202248 was a major identified residue in egg yolks and tissues, at ~6% TRR in muscle, ~26-28% TRR in egg yolk and fat, and 74-93% TRR in kidney and liver. Three other metabolites were identified: RPA 205834, in egg yolk (28% TRR); RPA 207048, in muscle and fat (49% and 21% TRR, respectively); and RPA 203328, in muscle (6% TRR).

The metabolism of isoxaflutole in livestock proceeds via hydrolysis of the isoxazole ring to form RPA 202248 and RPA 205834, followed by further hydrolysis to produce RPA 207048 and RPA 203328. HED concluded that livestock metabolism studies with isoxaflutole labeled in the isoxazole ring would not be required because metabolism was found to proceed via opening of the isoxazole ring.

Conclusions. The available data are adequate to satisfy data requirements; no additional livestock metabolism data are required to support the proposed use. HED has determined that the residues of concern in livestock commodities for risk assessment are isoxaflutole and metabolites RPA 202248, RPA 207048, and RPA 205834. For tolerance expression, isoxaflutole and RPA 202248 are the residues of concern.

860.1340 Residue Analytical Methods

DER Reference: 45655902.der.doc (also includes review of MRID 45655909)
MRID 44436001 (reviewed below)
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 228481, 8/20/96, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP#s 214199 and 214212, 12/7/95, P. Errico (PP#5G4484)

Plant commodities

Enforcement method: In conjunction with PP#6F04664, the petitioner proposed a GC/MSD method for the enforcement of tolerances for isoxaflutole and metabolites RPA 202248 and RPA 203328 in corn commodities. The method involves hydrolysis of isoxaflutole to RPA 202248, conversion of RPA 202248 to RPA 203328, and then derivatization of RPA 203328 to a methyl ester for GC analysis. Briefly, homogenized crop samples are extracted with methanol; crude and refined oil samples are mixed with hexane prior to methanol extraction. The combined extracts are mixed with 2% NaOH to hydrolyze isoxaflutole to RPA 202248. The mixture is concentrated to remove methanol, saturated NaCl solution is added, and the extract is sequentially washed with dichloromethane (twice) and petroleum ether. The aqueous phase is acidified with concentrated HCl and residues are partitioned into dichloromethane. The dichloromethane phase is then evaporated to dryness and hydrolyzed with 1 M methanolic NaOH solution (at 100 °C for one hour) to convert RPA 202248 residues to RPA 203328. Water is added, the mixture is acidified using concentrated HCl, and residues are partitioned into dichloromethane. Residues of RPA 203328 are derivatized to the methyl ester RPA 204497 using diazomethane. The derivatized extract is brought to volume with dichloromethane and analyzed by GC/MSD in the selective ion mode. Residues are reported as ppm isoxaflutole equivalents. The LOQ is 0.01 ppm.

Adequate validation data, including independent laboratory validation (ILV) and radiovalidation data, have also been submitted. An adequate interference study was conducted. The method has been validated by the Analytical Chemistry Branch (ACB) of the Biological and Economics Analysis Division (BEAD); however, minor revisions of the method were required. The petitioner submitted a revised version of the method in MRID 44436001. The method was revised to specifically address the issues identified by ACB. ACB had also requested that the petitioner demonstrate that a feasible alternative to diazomethane is not available; the petitioner responded that a study evaluating alternative procedures to diazomethane usage was submitted previously (MRID 43904829); no suitable alternatives to diazomethane were identified.

Data collection method: Bayer CropScience (formerly Rhône-Poulenc Ag Company) has submitted a method description and validation data for an LC/MS/MS method (CAL Study #019-03) entitled, "Method of Analysis for the Determination of RPA 201772 and its Metabolites (RPA 202248 and 203328) in Raw Agricultural Commodities and Processed Foods." A modified version of this method was used for data collection in samples of corn commodities from the crop field trial study submitted in conjunction with this registration request.

Briefly, raw agricultural and processed matrices are mixed with 1% formic acid and allowed to stand for 5-10 minutes. These mixtures are then extracted twice with methanol and the extracts are mixed with 1 N HCl and 10% sodium chloride and partitioned twice with dichloromethane

(DCM). The combined DCM phases are mixed with 1% formic acid, concentrated to remove the DCM, diluted with 1% formic acid, and cleaned up by solid-phase extraction (SPE). One fraction is eluted from the SPE column with 40% ACN in water and one fraction is eluted with 70% ACN in water; each fraction is diluted to volume with ACN and water. The first fraction is analyzed for residues of metabolites RPA 202248 and RPA 203328 using LC/MS/MS with a turbo ion-spray interface, and the second fraction is analyzed for residues of isoxaflutole using LC/MS/MS with a heated nebulizer interface. For both analyses, a C8 column with a gradient mobile phase of ACN and 1% acetic acid in water are used. The validated LOQ is 0.01 ppm for each analyte in each matrix.

Acceptable method validation recoveries were obtained for isoxaflutole, RPA 202248, and RPA 203328 from samples of corn grain and flour, wheat straw, and mustard foliage fortified at the LOQ and 10x the LOQ. Individual recoveries at each fortification level were within the acceptable range of 70-120%, with the exception of RPA 203328 in wheat straw at 0.10 ppm, which had four low recoveries (61.8-65.2%).

The fortification levels and samples used in method validation are not adequate to bracket expected residue levels in corn commodities. Concurrent recovery data were included with the crop field trial study submitted in conjunction with this registration request, in which samples were analyzed using a modified version of the LC/MS/MS method; the method was modified to remove the SPE cleanup steps and to add the use of internal standards for analyte quantification. Adequate concurrent recovery data were submitted for each analyte in corn forage, grain, and stover. **However, due to highly variable recoveries, this version of the method is unsuitable for tolerance enforcement. The residue data generated with version of the method is not adequate for tolerance-setting purposes.**

A successful ILV study reflecting adequate recoveries was submitted for corn grain fortified with isoxaflutole, RPA 202248, and RPA 203328 at 0.01 and 0.02 ppm. The ILV was conducted using a revised version of the method, CAL Study #019-03 (Revision 1). The differences between the revised and original versions of the method were very minor (a change in the speed used for centrifugation of samples in the initial extraction step, and addition of a potential substitute for the filter paper used for filtration).

No confirmatory analysis procedures were included in the method, and no interference study was submitted. Because the petitioner is not proposing the LC/MS/MS method for enforcement purposes, no confirmatory procedure or interference study is required.

No radiovalidation data were submitted for the LC/MS/MS method. The initial extraction procedures of the LC/MS/MS method are very similar to those of the previously proposed GC/MSD enforcement method, which has been adequately radiovalidated (refer to DP# 224213, 8/14/96, G. Kramer). These data are adequate to satisfy radiovalidation requirements for the LC/MS/MS method.

Conclusions. The available data are adequate to satisfy data requirements. An adequate method is available for the enforcement of tolerances for crop commodities. Samples of corn commodities from the submitted crop field trials were analyzed using a data-collection method adequate for the purposes of this action. The previously identified requirement to submit a revised version of the GC/MSD enforcement method is now fulfilled.

Livestock commodities

DER Reference: None
MRID 44506301 (reviewed below)
Residue Chemistry Memo DP# 238240, 11/26/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)

An HPLC/UV method has been submitted previously for the enforcement of tolerances for isoxaflutole residues in livestock commodities. Milk samples are extracted in acidified ACN, the extract is purified on a C8 cartridge column, and RPA 203328 is eluted in the first fraction and isoxaflutole, RPA 205834 and RPA 202248 are eluted in the second. The two fractions are then analyzed on two different HPLC/UV systems, both of which employ a C18 column with UV detection (270 or 300 nm). Egg samples are extracted in ACN and the extract purified on a C8 cartridge column; RPA 202248 is eluted from the column and analyzed by HPLC/UV as described above. Tissue samples are analyzed by a common moiety technique. The samples are extracted in 0.1% aqueous trifluoroacetic acid. The extracts of fat samples are partitioned against hexane. In all samples, isoxaflutole is converted to RPA 202248 by base hydrolysis. The extract is then purified on a C18 cartridge column. RPA 202248 is eluted and analyzed by HPLC/UV as described above. The method includes conditions for separation on a different HPLC column as a confirmatory technique. The LOQs are 0.01 ppm for each analyte in milk, 0.01 ppm for eggs, 0.20 ppm for beef and poultry muscle and fat, 0.20 ppm for beef kidney, and 0.40 ppm for beef and poultry liver.

Adequate validation data, including ILV and radiovalidation data, have also been submitted. An adequate interference study was conducted. The method has been validated by ACB; however, minor revisions of the method were required. The petitioner submitted a revised version of the method in MRID 44506301. The method was revised to address the issues identified by ACB. ACB had suggested that the petitioner either modify the milk extraction procedures to match the common moiety procedures used for tissues, or amend the method to include instructions to test each batch of the C8 cartridges for recovery of the parent and metabolite. The petitioner chose to add instructions to test the C8 cartridges.

Conclusions. The available data are adequate to satisfy data requirements. The previously identified requirement to submit a revised version of the HPLC/UV enforcement method is now fulfilled.

HED notes that the method only includes instructions for the determination of RPA 202248 in egg samples; isoxaflutole is not determined in eggs using this method. This is appropriate as the results of the storage stability and poultry feeding studies indicated that any isoxaflutole in eggs is immediately converted to RPA 202248.

860.1360 Multiresidue Methods

The FDA PESTDATA database (dated 06/05) indicates that isoxaflutole is not recovered by Multiresidue Methods Section 302 (Luke method; Protocol D) and is partially recovered using Section 303 (Mills, Onley, Gaither method; Protocol E, nonfatty; 60-120% recovery) and Section 304 (Mills fatty food method; Protocol F, fatty; 37-126% recovery). Metabolite RPA 202248 is

not recovered using Sections 302, 303, or 304, and metabolite RPA 203328 is not recovered using Section 402 (Protocol B).

860.1380 Storage Stability

DER Reference: 44169006.der.doc
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)

Storage stability data have been submitted previously which indicate that weathered total residues of isoxaflutole, RPA 202248, and RPA 203328 are stable in/on corn grain, forage, fodder, and silage during frozen storage (<-10 °C) up to 13 months, and that fortified residues of isoxaflutole, RPA 202248, and RPA 203328 are stable in/on corn flour, meal, grits, starch, and refined oil during frozen storage (<-10 °C) for up to 3 months.

In addition, Bayer CropScience (formerly Rhone-Poulenc Ag Company) has submitted the results of a storage stability study with isoxaflutole and its metabolites RPA 202248 and 203328 in field corn commodities. Samples of untreated corn silage, fodder, and grain were fortified separately with isoxaflutole, RPA 202248, or RPA 203328 at 0.210 ppm for each analyte for silage and fodder and 0.105 ppm for each analyte for grain. All samples were stored frozen (<-10 °C) and analyzed at intervals of 0, 1, 2, 3, 6, 12, and 15 months.

Samples were analyzed for residues of isoxaflutole, RPA 202248, and 203328 using the GC/MSD enforcement method. The method was adequate for data collection based on acceptable concurrent method recoveries. The LOQ was 0.01 ppm for each analyte in each commodity.

The results indicate that fortified residues of isoxaflutole, RPA 202248, and RPA 203328 are relatively stable in/on field corn silage, fodder, and grain stored frozen for up to 15 months.

The storage durations and conditions of samples from the crop field trials submitted to support this petition are presented in Table 6.

Table 6. Summary of Storage Conditions and Durations of Samples from Crop Field Trial Studies.

Matrix	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Early Forage	<-15	180-593 days (5.9-19.5 months)	Weathered total residues of isoxaflutole, RPA 203328, and RPA 202248 are stable in/on field corn forage, grain, and stover during frozen storage for up to 13 months. Fortified residues of isoxaflutole, RPA 202248, and RPA 203328 are stable in/on field corn silage, fodder, and grain during up to 15 months of frozen storage.
Forage		145-563 days (4.8-18.5 months)	
Grain		128-545 days (4.2-17.9 months)	
Stover		137-552 days (4.5-18.2 months)	

Adequate storage stability data have also been submitted for livestock commodities. Samples of egg, milk, and cattle liver, kidney, muscle, and fat were fortified with residues of isoxaflutole,

RPA 202248, RPA 205834, RPA 207048, and RPA 203328 and stored frozen (<-10 °C) for 4 months. The results for milk indicated that RPA 202248, RPA 205834 and RPA 203328 are stable during 4 months of frozen storage; isoxaflutole appeared to degrade with an estimated half life of approximately 111 days. The results for tissues indicated that RPA 207048 does degrade in some tissue matrices; the other analytes appeared to be stable in the kidney, muscle, and fat tissues. For liver, isoxaflutole and RPA 202248 appeared to be generally stable, whereas RPA 205834 and RPA 207048 appeared to degrade with an estimated half life of about 3 months. The results for egg indicated that RPA 202248 is stable during frozen storage; isoxaflutole was immediately converted to RPA 202248 in egg.

Conclusions. The available data are adequate to satisfy data requirements. Adequate storage stability data are available to support the crop field trial study submitted with this registration request. These data indicate that no correction for decline during storage is needed for field corn commodities.

860.1480 Meat, Milk, Poultry, and Eggs

DER Reference: None
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)

HED had previously calculated the dietary burdens of isoxaflutole to livestock to be 1.42 ppm for dairy cattle, 1.23 ppm for beef cattle, and 0.20 ppm for poultry, based on the established tolerances for isoxaflutole residues in/on field corn commodities. Because the submitted field trial data indicate that no changes to the existing field corn tolerances are needed, the proposed uses do not change the estimated dietary burdens of isoxaflutole to livestock.

No feeding studies were submitted with this registration request. Adequate feeding studies with cattle and poultry were submitted previously. Based on the results of the study and the residues of concern in livestock commodities, HED concluded that tolerances were needed for the combined residues of isoxaflutole and RPA 202248 in eggs at 0.01 ppm; milk at 0.02 ppm; meat and fat of cattle, goat, hog, horse, poultry, and sheep at 0.20 ppm; meat byproducts of cattle, goat, hog, horse, and sheep at 0.10 ppm; poultry liver at 0.30 ppm; and liver of cattle, goat, hog, horse, and sheep at 0.50 ppm.

Conclusions. The available livestock feeding study data are adequate to satisfy data requirements. Because the proposed use does not change the estimated dietary burdens of isoxaflutole to livestock, HED concludes that the established tolerances for livestock commodities are adequate to support the proposed uses. No revisions in the tolerances for livestock commodities are needed.

860.1500 Crop Field Trials

DER Reference: 47114035.der.doc
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP#s 214199 and 214212, 12/7/95, P. Errico (PP#5G4484)

Bayer CropScience has previously submitted adequate crop field trial data reflecting preemergence application of a WDG formulation of isoxaflutole at 0.223 lb ai/A (1.2x the maximum seasonal rate on current product labels). The maximum total residues of isoxaflutole, RPA 202248, and RPA 203328 were 0.88 ppm in forage, 0.40 ppm in fodder, and 0.11 ppm in grain. These data were used to establish the existing tolerances for field corn commodities at 1.0 ppm for forage, 0.5 ppm for stover, and 0.2 ppm for grain.

Bayer CropScience has submitted field trial data for isoxaflutole on field corn when applied with the safener cyprosulfamide (MRID 47114035) as an early postemergence application. Twenty field trials were conducted in the U.S. in Zones 1 (VA; 1 trial), 2 (GA; 1 trial), 5 (IA, IL, IN, KS, MN, MO, NE, ND, OH, WI; 17 trials), and 6 (TX; 1 trial) during the 2005 growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500 for field corn.

Each trial consisted of one untreated plot and one treated plot. Field corn received one foliar broadcast application of a 2.0 lb/gal FlC formulation at a rate of 0.113-0.122 lb ai/A (~0.8x the proposed maximum seasonal rate). The test substance also contained safener cyprosulfamide at 2.0 lb/gal. Applications were made at growth stage BBCH 12 (two leaves unfolded) at 19 of the trials and at growth stage BBCH 13 (three leaves unfolded) at 1 trial. All applications were made using ground equipment in spray volumes of 10-20 gal/A without an adjuvant. Samples of early field corn forage were collected at a PHI of 43-45 days. Samples of field corn forage were collected at earliest commercial harvest (BBCH 85-87), 67-118 days after application, and samples of field corn grain and fodder (stover) were collected at maturity (BBCH 89), 91-157 days after application. Additional samples of early forage were collected from two trial sites at 30-31, 37-38, 51, and 58-59 days after application to generate residue decline data.

Samples of field corn were analyzed for residues of isoxaflutole and its metabolites RPA 203328 and RPA 202248 using a modified version of LC/MS/MS CAL Study #019-03 (Revision 1). The validated LOQ was 0.01 ppm for each analyte. The method was adequate for data collection based on acceptable concurrent method recoveries. The available storage stability data are adequate to support the storage conditions and durations of samples from the corn field trials.

The results of the crop field trials are presented in Table 8. Residues of isoxaflutole were below the LOQ in/on all samples of early forage, grain, and stover, and in/on 38 of 40 forage samples; quantifiable residues of isoxaflutole were observed in/on two forage samples at 0.015 ppm. Residues of RPA 203328 were <0.010-0.071 ppm in/on early forage, <0.010-0.084 ppm in/on forage, <0.010-0.033 ppm in/on grain, and <0.010-0.160 ppm in/on stover. Residues of RPA 202248 were below the LOQ in/on all samples of early forage, grain, and stover, and in/on 38 of 40 forage samples; quantifiable residues of RPA 202248 were observed in/on two forage samples at 0.014 ppm. Combined residues (isoxaflutole + RPA 203328 + RPA 202248) were <0.030-<0.091 ppm in/on early forage, <0.030-0.113 ppm in/on forage, <0.030-<0.053 ppm in/on grain, and <0.030-<0.180 ppm in/on stover.

The residue decline data indicated that combined residues of isoxaflutole, RPA 203328, and RPA 202248 do not increase substantially in/on corn early forage with increasing sampling intervals. In one trial, residues increased slightly from the 31-day sampling interval (average of 0.050 ppm) to the 45-day sampling interval (average of 0.074 ppm) and then remained constant. In the second trial, residues were approximately the same at each sampling interval.

Table 8. Summary of Residue Data from Crop Field Trials with Isoxaflutole.

Crop matrix	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.[2]
FIELD CORN (proposed use = 0.141 lb ai/A total application rate, 45-day PHI)									
Isoxaflutole									
Early Forage	0.113-0.122	43-45	40	<0.010	<0.010	0.010	0.010	0.010	NA
Forage	0.113-0.122	67-118	40	<0.010	0.015	0.015	0.010	0.010	0.001
Grain	0.113-0.122	91-157	40	<0.010	<0.010	0.010	0.010	0.010	NA
Stover	0.113-0.122	91-157	40	<0.010	<0.010	0.010	0.010	0.010	NA
RPA 203328									
Early Forage	0.113-0.122	43-45	40	<0.010	0.071	0.065	0.013	0.022	0.019
Forage	0.113-0.122	67-118	40	<0.010	0.084	0.069	0.012	0.023	0.019
Grain	0.113-0.122	91-157	40	<0.010	0.033	0.030	0.010	0.012	0.006
Stover	0.113-0.122	91-157	40	<0.010	0.160	0.133	0.010	0.024	0.031
RPA 202248									
Early Forage	0.113-0.122	43-45	40	<0.010	<0.010	0.010	0.010	0.010	NA
Forage	0.113-0.122	67-118	40	<0.010	0.014	0.014	0.010	0.010	0.001
Grain	0.113-0.122	91-157	40	<0.010	<0.010	0.010	0.010	0.010	NA
Stover	0.113-0.122	91-157	40	<0.010	<0.010	0.010	0.010	0.010	NA
Combined Residues (isoxaflutole + RPA 203328 + RPA 202248)									
Early Forage	0.113-0.122	43-45	40	<0.030	<0.091	0.085	0.033	0.042	0.019
Forage	0.113-0.122	67-118	40	<0.030	0.113	0.098	0.032	0.044	0.020
Grain	0.113-0.122	91-157	40	<0.030	<0.053	0.050	0.030	0.032	0.006
Stover	0.113-0.122	91-157	40	<0.030	<0.180	0.153	0.030	0.044	0.031

[1] HAFT = Highest-average field trial result.
[2] NA = Not applicable.

Conclusions. The submitted field corn field trial data are adequate to satisfy data requirements. Although the crop field trial data reflect application at ~0.8x the proposed maximum seasonal rate, HED concludes that the data are adequate to support the proposed use. The maximum residues in/on forage, grain, and stover were well below the established tolerances for these commodities; therefore, it is unlikely that application at 1x would yield residues above the established tolerances. Also, due to highly variable recoveries, the version of the method used in these trials is unsuitable for tolerance enforcement. The residue data generated with version of the method is not adequate for tolerance-setting purposes, but is adequate to demonstrate that residues will not exceed the established tolerances.

No field trial data were submitted reflecting preplant or preemergence application in combination with postemergence application. These data will not be required at this time because the proposed labels specify that the maximum total seasonal application rate from all sources is 0.14

lb ai/A when postemergence applications are made. On the existing product labels, the maximum seasonal rate is 0.19 lb ai/A for preplant/preemergence applications. The existing tolerances were established using field trial data reflecting preemergence applications at up to 0.223 lb ai/A. HED concludes that because field trial data are available reflecting preemergence application at rates up to ~1.6x the application rates proposed with this registration request, field trial data reflecting preemergence applications in combination with postemergence applications will not be required to support the proposed uses.

Residue data for field corn aspirated grain fractions were submitted previously with a processing study; see 860.1520.

The established tolerances for field corn commodities are adequate to support the proposed uses of isoxaflutole.

860.1520 Processed Food and Feed

DER Reference: None
Residue Chemistry Memo DP#s 214199 and 214212, 12/7/95, P. Errico (PP#5G4484)

A processing study with field corn was submitted previously. Following preemergence application of a WP formulation at 0.67 lb ai/A (the highest rate which exhibited no phytotoxicity; 4.8x the proposed maximum seasonal rate for the current submission), samples of field corn grain were collected and processed using wet- and dry-milling procedures into starch, crude oil, and refined oil (wet milling), or into grits, flour, meal, crude oil and refined oil (dry milling). Aspirated grain fractions were also generated. Samples were analyzed for total residues of isoxaflutole, RPA 202248, and RPA 203328 using the GC/MSD common moiety method. The results of the study indicate that total residues of isoxaflutole, RPA 202248, and RPA 203328 do not concentrate in aspirated grain fractions, grits, meal, flour, starch, crude oil, or refined oil. No tolerances for the processed commodities of field corn are needed.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for isoxaflutole and its metabolites RPA 202248 and RPA 203328 are currently available in the EPA National Pesticide Standards Repository (personal communication with Dallas Wright, ACB, 1/30/08); the expiration dates are 8/26/12, 2/23/10, and 9/27/09, respectively. In addition, a reference standard is available for RPA 204497 (the methyl ester of RPA 203328), which is the compound determined in the GC/MSD enforcement method; the expiration date is 8/21/08.

860.1850 Confined Accumulation in Rotational Crops

DER Reference: None
Residue Chemistry Memo DP# 232139, 7/14/97, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 224213, 8/14/96, G.F. Kramer (PP#6F04664)

No confined rotational crop studies were submitted with this registration request. A confined rotational crop study with isoxaflutole labeled in the phenyl ring was submitted previously. In separate plots, [^{14}C]isoxaflutole was applied to the soil at 0.18 lb ai/A using preplant incorporated or preemergence applications. Representative crops of leafy vegetables (lettuce or mustard), root crops (radish), and cereal grains (sorghum or wheat) were planted 34, 123, and 365 days after treatment. TRR were >0.01 ppm in/on all rotational crop commodities, except radish root, from the 34-day PBI. At the 123-day PBI, TRR were >0.01 ppm in/on rotational wheat commodities only. At the 365-day PBI, TRR were ≥0.01 ppm in/on lettuce, radish leaf, and sorghum forage and stover.

Crop commodities with TRR ≥0.01 ppm were subjected to residue characterization and identification procedures. The major identified metabolite in all rotational crop commodities, except 34-day PBI radish leaf, was RPA 203328, at ~37-100% TRR. The major metabolite in 34-day PBI radish leaf was RPA 202248 (~27% TRR); RPA 202248 was also identified in 34-day PBI sorghum grain (<6% TRR). Isoxaflutole was not identified in any rotational crop commodity. HED concluded that a rotational crop study with isoxaflutole labeled in the isoxazole ring would not be required, because isoxaflutole metabolism was shown to proceed to opening of the isoxazole ring.

The petitioner submitted supporting storage stability data for the confined rotational crop study in which samples of rotational crop commodities were fortified with isoxaflutole, RPA 202248, and RPA 203328 and stored frozen. These data indicated that isoxaflutole extensively metabolized to RPA 202248 and RPA 203328 during storage. Although the stability of the metabolite profile was not investigated, HED concluded that an additional confined rotational crop study would not be required because the enforcement method determines residues of RPA 202248 and RPA 203328. HED also concluded that due to uncertainties in the composition of samples at harvest, the need for field rotational crop studies for isoxaflutole would be based on TRR values in the confined study (and not ppm values for the residues of concern). Because TRR were ≥0.01 ppm in/on all crops at the 12-month PBI, it was concluded that field rotational crop studies were required.

Conclusions. The available data are adequate to satisfy data requirements; no additional confined rotational crop data are needed to support the proposed use. HED has determined that the residues of concern in rotational crop commodities are isoxaflutole and its metabolites RPA 202248 and RPA 203328.

860.1900 Field Accumulation in Rotational Crops

DER Reference: None
Residue Chemistry Memo DP# 269319, 11/9/00, G.F. Kramer (PP#6F04664)
Residue Chemistry Memo DP# 263994, 8/4/00, G.F. Kramer (PP#6F04664)

No field rotational crop studies were submitted with this registration request. An adequate limited field rotational crop study has been submitted previously. In the study, a 75.1% WDG formulation was applied once at 0.14 lb ai/A (1x the proposed maximum seasonal rate for the current submission) to bare ground after planting corn (the primary crop) and prior to crop emergence; application was made in two separate trials in IL and OH. The treated plot in each trial location was divided into subplots to represent 29-30, 104-120, 151-180, or 365 PBIs. Representative crops of leafy vegetables (mustard), root crops (turnip or radish), and cereal grains (soybean, sorghum, or winter wheat) were then planted at each plot. The combined residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 were detectable in/on soybean hay (0.035-0.050 ppm) and soybean forage (0.010-0.014 ppm) collected from the OH plot representing the 30-day PBI. However, the combined residues were below 0.01 ppm in/on all rotational crop matrices collected from plots representing PBIs of 104-120, 151-180, and 365 days. Based on these results, HED concluded that a 6-month PBI for rotational crops was appropriate, and that tolerances for residues in rotational crop commodities would not be needed.

HED later concluded that a 4-month PBI for wheat would be appropriate (DP# 269805, 11/16/00, G.F. Kramer).

Conclusions. The available data are adequate to satisfy data requirements. The petitioner has proposed a 0-month PBI for field corn, a 4-month PBI for wheat, and PBIs of ≥6 months for other crops; these PBIs are identical to existing rotational crop restrictions. HED concludes that the proposed rotational crop restrictions are adequate for the purposes of this Section 3 request. HED assumes that all proposed plantback intervals greater than six months are needed due to phytotoxicity concerns and/or the other active ingredients in the products.

860.1550 Proposed Tolerances

Bayer CropScience has not proposed any new tolerances or tolerance revisions with this registration request.

Tolerances have been established for residues of isoxaflutole under 40 CFR 180.537. Tolerances are currently established under 180.537(a)(1) for combined residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328, calculated as the parent compound, in/on field corn forage, grain, and stover, at 1.0, 0.20, and 0.50 ppm, respectively. Tolerances have also been established under 180.537(a)(2) for combined residues of isoxaflutole and RPA 202248, calculated as the parent compound, in livestock commodities, at 0.01 ppm for egg; 0.02 ppm for milk; 0.10 ppm for the meat byproducts, except liver, of cattle, goat, hog, horse, and sheep; 0.20 ppm for the fat and meat of cattle, goat, hog, horse, poultry, and sheep; 0.30 ppm for poultry liver; and 0.50 ppm for the liver of cattle, goat, hog, horse, and sheep.

The available data indicate that the requested uses of isoxaflutole do not require any changes in the established tolerances for field corn or livestock commodities.

References

DP#: 214199 and 214212
Subject: 264-EUP-00/PP#5G4484. Proposed Temporary Tolerance Request For Isoxaflutole in/on Field Corn Grain. Evaluation of Analytical Method and Residue Data. CBTS#'s 15430 & 15431.
From: P. Errico
To: D. Kenny/J. Miller
Date: 12/7/95
MRIDs: 43573201-43573208, 43573249-43573253, and 43588003

DP#: 224213
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn and animal RACs. Evaluation of Residue Data and Analytical Methods. Chemical 123000. CBTS# 17015. Case 287353.
From: G.F. Kramer
To: C. Eiden/D. McCall
Dated: 8/14/96
MRIDs: 43904801, 43904802, 43904827-43904837, and 43904839

DP#: 228481
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn. Results of Petition Method Validation (PMV). Chemical 123000. CBTS# 17413.
From: G.F. Kramer
To: C. Eiden/D. McCall
Dated: 8/20/96
MRIDs: 43573251

DP#: 232139
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. Amendment of 12/2/96. Revised Sections B & F, New Analytical Method for Animal Tissues and Storage Stability Data. Chemical 123000. Case 287353.
From: G.F. Kramer
To: B. Madden
Dated: 7/14/97
MRIDs: 44169001-44169007

DP#: 238728
Subject: HED Metabolism Assessment Review Committee Meeting of 9/4/97. Isoxaflutole. PP# 6F04664. Chemical 123000.
From: G.F. Kramer
To: HED Metabolism Committee Members
Dated: 9/25/97

DP#: 238240
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. Amendments of 8/12/97 & 9/25/97. Revised Sections B & F. Chemical 123000. Case 287353.
From: G.F. Kramer
To: B. Madden
Dated: 11/26/97

DP#: 263994
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn and Livestock Commodities. Evaluation Of A Limited Field Rotational Crop Study. Chemical 123000. Case 046754. Submission S574572.
From: G.F. Kramer
To: D. Kenny/J. Miller
Dated: 8/4/00
MRID: 45021201

DP#: 269319
Subject: PP# 6F04664. Isoxaflutole in/on Field Corn and Livestock Commodities. Evaluation Of A Limited Field Rotational Crop Study. Review of Amendment Dated 9/22/00 Submitted in Response to HED's Memo of 8/4/00. Chemical 123000. Case 046754. Submission S585916.
From: G.F. Kramer
To: D. Kenny/J. Miller
Dated: 11/9/00
MRID: 45216301

DP#: 269805
Subject: ID# 000264-00567. Review of Label Amendment for Isoxaflutole (Balance WDG Herbicide). Chemical 123000. Case 046752. Submission S586621.
From: G.F. Kramer
To: S. Stanton/J. Miller
Dated: 11/16/00

cc: G. Kramer (RAB1)
RDI: RAB1 Chemists (4/2/08)
G.F. Kramer:S10781:PY-S:(703)305-5079:7509P:RAB1

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